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Original Article

Diagnostic Yield of Pleural Fluid Cytology in Malignant Pleural Effusion

Marrium Asim and Nasir Saleem

Department of Pathology, Pakistan Institute of Medical Sciences, Islamabad

Abstract

Background: Pleural effusion is a common presenting feature of patients presenting in the pulmonology OPD. Examination of pleural fluid obtained by thoracocentesis is a simple way to diagnose pathologies of the pleura and peripheral parts of the lung.

Objective: To determine the diagnostic yield of pleural fluid cytology in malignant pleural effusions keeping pleural biopsy as the gold standard.

Materials and Method: This retrospective study was carried out at Pakistan Institute of Medical Sciences, Islamabad, from November 2010 to November 2011. Twenty six patients (65% females; 35% males) presenting with pleural effusion in whom pleural fluid cytology with concurrent pleural biopsy was carried out were included in the study. The diagnostic yield of pleural fluid was determined keeping pleural biopsy as the gold standard.

Results: The age range of the patients was 23-76 years. Pleural fluid was positive for malignant cells in 15 out of 26 patients, whereas pleural biopsy yielded definite evidence of malignancy in 21 cases. In 5 cases diagnosis of atypical infiltrate was rendered and immunohistochemistry was suggested for confirmation of malignancy. The diagnostic yield of pleural fluid cytology came out to be 58%.

Conclusion: Pleural fluid cytological examination followed by pleural biopsy remains the initial diagnostic procedure in management of patients with suspected malignant pleural effusion.

Keyword: Pleural fluid cytology, pleural effusion, thoracocentesis, malignant pleural effusion.

Introduction

Pleural effusion is a common feature in patients presenting in any pulmonology department. Based on laboratory findings, it is of two types i.e. transudative and exudative. Transudative type of effusion is caused by congestive heart failure, nephrotic syndrome, cirrhosis and lymphatic obstruction by a tumor. Most common causes of exudative pleural effusion in our country are pulmonary tuberculosis followed by malignancy.[1,2] Malignancy is not only a consideration in the elderly but also in the younger patients. It is exudative in nature, and poses a diagnostic challenge to the treating physicians.

Malignant pleural effusions are most commonly caused by carcinomas of breast, lung, gastrointestinal tract, ovary and hematological malignancies. In males the most common cause of malignant pleural effusion is lung cancer followed by lymphoma and leukemia. In females the leading cause is carcinoma of breast followed by female genital tract malignancies and primary lung carcinomas.[3]

The most commonly carried out procedure in the initial investigation of patients with pleural effusion is thoracocentesis which may be followed by blind percutaneous pleural biopsy or thoracoscopic pleural biopsy if the effusion is exudative in nature. Thoracoscopy is the procedure of choice in patients with suspected malignant pleural effusion, in whom cytology is negative. In this study we evaluated the diagnostic yield of pleural fluid cytology in malignant pleural effusion in our set up.

Materials and Methods

This was a retrospective, observational study carried out at Pakistan Institute of Medical Sciences, Islamabad. Nonprobability, consecutive type of sampling was done in which cases were taken out from the surgical pathology files of patients in whom pleural fluid cytology and pleural biopsy had been carried out between October 2010 and October 2011. Patient's clinical history or radiological findings were not taken into account as they were not available in all cases.

Inclusion criteria:

1. A pleural biopsy showing definitive evidence of malignancy.
2. Patients in whom pleural fluid cytology and subsequently pleural biopsy was carried out

Exclusion criteria:

1. Non diagnostic pleural fluid cytology.
2. Non diagnostic pleural biopsy.

Pleural fluid preparation

The pleural fluid submitted for cytological examination was centrifuged and subsequently two slides were made. The slides were stained with hematoxylin and eosin. On microscopic examination, the findings were stratified in four diagnostic categories; Category 1: No malignant cells seen. Category 2: Atypical cells seen. Category 3: Atypical cells suspicious of malignancy and Category 4: Malignant cells seen. Cells designated as; 'Atypical' were the ones having hyperchromatic nuclei, exhibiting variable degree of pleomorphism and variable amount of cytoplasm, but the features fell short of clear cut evidence of malignancy. Malignant cells were defined as cells exhibiting marked pleomorphism, having hyperchromatic nuclei and high N/C ratio.

Pleural biopsy preparation

The pleural biopsy specimens received were fixed in 10% formalin, embedded in paraffin wax after completion of processing and subsequently stained with hematoxylin and eosin. On microscopic examination two diagnostic categories were made; Category 1: Cases in which there was a definitive evidence of malignancy and Category 2: Cases which showed atypical infiltrate suggestive of malignancy.

The cases in Category 1 showed variable arrangement of malignant cells which may be in the form of sheets or glandular arrangement with the cells exhibiting marked pleomorphism, having hyperchromatic nuclei and high N/C ratio. Cases in Category 2 revealed cells exhibiting pleomorphism and having hyperchromatic nuclei and high N/C ratio but either due to scanty nature of biopsy or questionable invasion, with features falling short of clear cut evidence of malignancy. The cytology and the biopsy cases were examined by a senior resident and a consultant histopathologist at two different occasions and allocated a category so as to remove any bias.

All data were analyzed using Statistical Package for Social Sciences (SPSS) version 10 for this study. For numerical data mean and standard deviation were determined. Qualitative data e.g. gender were expressed in terms of frequency. At the end diagnostic yield was calculated (total number of cases positive in cytology divided by the total number of cytology cases).

Results

The total number of patients was 26. The age range of the patients was 23-76 years, with the mean age being 55.6±12.7 SD years. The median age was 55.5 years. The gender distribution showed a female predominance (Figure 1). Most of the female patients of malignant pleural effusion were middle aged, whereas male patients with malignant pleural effusion were elderly (Figure 2).

The distribution of cytological diagnosis in each category is shown in Table 1.

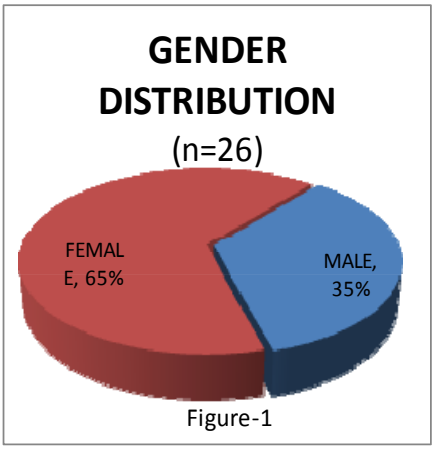

Figure-1

Most of the cases belonged to the category 1 (negative for malignant cells). All cases belonging to category 2, 3 & 4 were assigned as positive for malignancy. In routine practice as well, all cases diagnosed as malignant or atypical are investigated further in the work up for malignant cases. Based on these criteria the number of positive cases on cytology was 15 out of 26 (58%).

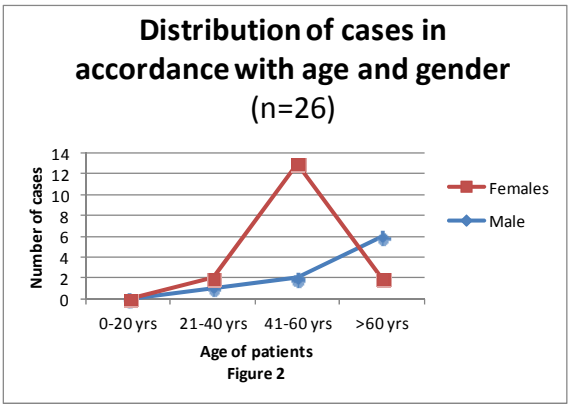

Figure 2

Pleural biopsy provided conclusive evidence of malignancy in 21 cases and these cases were placed in category 1 (Malignant). In 3 out of 21 cases, diagnosis of mesothelioma was favored and in 8 cases the diagnosis of adenocarcinoma was favored. In the rest of 10 cases a diagnosis of malignant neoplasm was made and immunohistochemistry was suggested for confirmation of diagnosis. 5 cases belonged to category 2 (atypical infiltrate suggestive of malignancy) and comment was made that immunohistochemistry was required for confirmation of diagnosis and exact subtyping of tumor. Amongst these 5 cases, two cases were cytologically negative for malignancy. Each of the remaining three cases was cytologically categorized as belonging to category 2, 3 and 4. Of the cases that were diagnosed as malignant neoplasm on biopsy there were nine cases in which cytology was negative for malignancy, eight cases belonged to category 4, two cases placed in category 3 and one case to category 2.

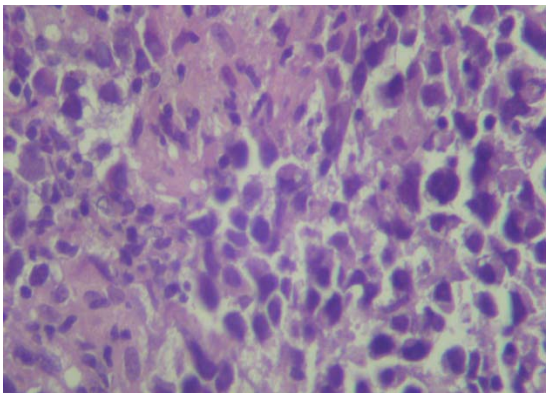

Fig.3: Malignant neoplasm

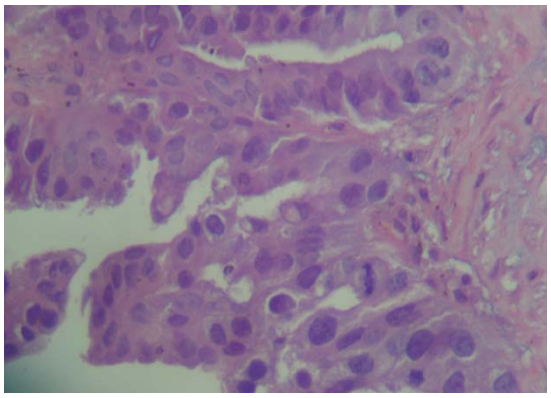

Fig 4:Malignant neoplasm suggestive of mesothelioma

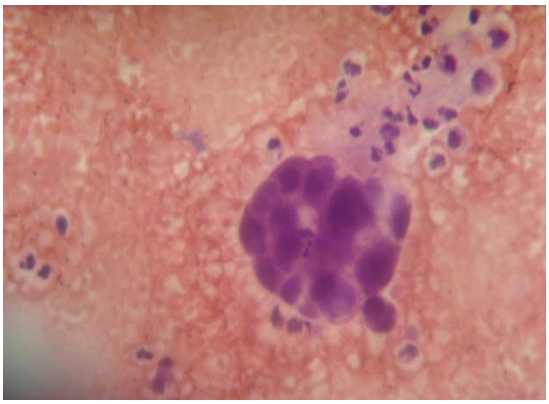

Fig.5: Malignant cells – category 3

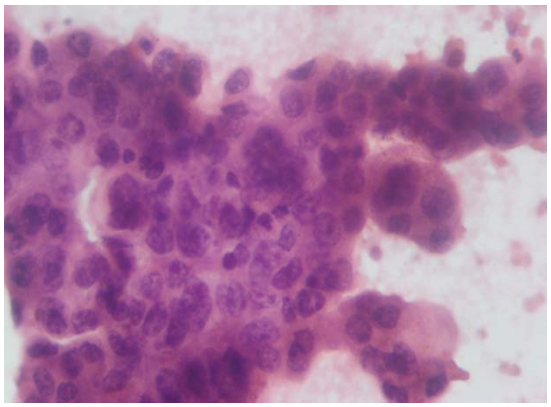

Fig.6: Atypical cells - category 4

Table 1. Distribution of cytology cases	
Category of cytological cases	Number of cases (%)
Category 1	11 (42.3)
Category 2	2 (7.7)
Category 3	4 (5.4)
Category 4	9 (34.6)

Immunohistochemistry was suggested for definitive diagnosis in cases in which a diagnosis of adenocarcinoma or mesothelioma was favored. Immunohistochemical markers required for this differentiation were not available at our center during the period of study, therefore these cases were referred to other specialized centers.

Discussion

The annual incidence of malignant pleural effusion in USA is 150,000 cases.[4]The cytological examination of the pleural fluid is the investigation of choice in patients with suspicion of malignant pleural effusion (MPE) as it is a simple and rapid procedure. Not all the pleural effusions developing in a patient of known malignancy are malignant. Some are negative on cytology as well as biopsy. These are termed as paramalignant effusion. The reasons for development of a paramalignant effusion include: bronchial obstruction, lymphatic duct obstruction, post obstruction pneumonitis, lymph node enlargement and pulmonary emboli. Other causes of pleural effusion include underlying cardiac disease, liver disease and renal disease, these are termed as nonmalignant effusions.

Establishment of the exact cause of MPE is very important as the mean survival of the patient following a diagnosis of malignant pleural effusion is 3-6 months. Furthermore, it is an indicator of surgical incurability and precludes the need for further investigations.[5] In contrast, paramalignant pleural effusion may be amenable to surgical resection and non malignant pleural effusion may be treated by treating the underlying disease.

This study highlights the importance of initial pleural fluid cytological examination in patients suspected of having a malignant pleural effusion. The diagnostic yield in our study was 58%. In a study carried out by Ong KC et al on 103 patients, positive results of initial pleural fluid cytological examination was 48.5%.[6] Various studies have shown different diagnostic yields of pleural fluid cytology ranging from 60-90%.[7]A study done in Pakistan on 150 patients revealed a very low diagnostic yield i.e. 8%.[8]Despite the development of new diagnostic procedures cytological examination of the pleural fluid followed by closed pleural biopsy remain the initial diagnostic procedures,

thoracoscopy being reserved for cases not diagnosed by closed pleural biopsy. [9]

Several factors have been shown to influence the diagnostic yields in various reports. To begin with the different proportions of malignant, para malignant and non malignant cases affect the yield of fluid cytology in a manner such that if the study has a majority of non malignant cases then the diagnostic yield that will come at end will be small. Then, location and type of tumor also has a great influence on whether the cytology will be negative or positive. A tumor located in the central bronchi which are mostly squamous cell carcinoma or small cell carcinoma is less likely to produce a malignant effusion as compared to peripherally situated adenocarcinomas. Other factors which influence the diagnostic yield include specimen handling, volume of fluid submitted and extent of pleural involvement. Quick sample processing that is within half an hour after reception of the sample along with preparation of cell blocks significantly increases the yield. Different studies have highlighted that at least 30 ml of pleural fluid must be submitted and the entire sample must be processed in order maximize the yield. In our study the quantity of fluid submitted was approximately 5 ml. Finally it is said that, greater the extent of pleural involvement greater the probability that cytology will be positive.

Despite all the above mentioned factors responsible for variation in diagnostic yield of pleural fluid cytology it is still the procedure of choice in patient with suspicion of malignant pleural effusion, as it is simple cost effective procedure which can be performed on out-patient basis without any major complication and it has a yield which is comparable to that of pleural biopsy.[10,11] The major drawbacks of this study are a small sample size and its retrospective nature. However, there was no bias in this study as the cytology and the biopsy cases were examined by two different pathologists at two different occasions and allocation of cases to each category was not influenced by any information provided by the physician.

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